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Very preterm infants show earlier emergence of 24-hour sleep–wake rhythms compared to term infants

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ABSTRACT

Background: Previous studies show contradictory results about the emergence of 24-h rhythms and the influence of external time cues on sleep–wake behavior in preterm compared to term infants.
Aims: To examine whether very preterm infants (<32 weeks of gestational age) differ in their emergence of the 24-h sleep–wake rhythm at 5, 11 and 25 weeks corrected age compared to term infants and whether cycled light conditions during neonatal intermediate care affects postnatal 24-h sleep–wake rhythms in preterm infants.
Study design: Prospective cohort study with nested interventional trial.
Subjects: 34 preterm and 14 control term infants were studied. During neonatal hospitalization, preterm infants were randomly assigned to cycled light [7 am–7 pm lights on, 7 pm–7 am lights off, n = 17] or dim light condition [lights off whenever the child is asleep, n = 17].
Outcome measures: Sleep and activity behavior recorded by parental diary and actigraphy at 5, 11 and 25 weeks corrected age.
Results: Sleep at nighttime and the longest consolidated sleep period between 12 pm-6 am was longer (mixed model analysis, factor group: $p = 0.02$, resp. $p = 0.01$) and activity at nighttime was lower ($p = 0.005$) at all ages in preterm compared to term infants. Cycled light exposed preterm infants showed the longest nighttime sleep duration. Dim light exposed preterm infants were the least active.
Conclusions: Preterm infants show an earlier emergence of the 24-h sleep–wake rhythm compared to term infants. Thus, the length of exposure to external time cues such as light may be important for the maturation of infant sleep–wake rhythms.
Trial registry number: This trial has been registered at www.clinicaltrials.gov (identifier NCT01513226).

1. Introduction

In a term newborn, sleep is evenly distributed across day and night [1]. At around 6 weeks of age, 24-h sleep–wake rhythms can be detected in most infants represented by a shift of sleep periods into the nighttime and wake periods into daytime [1,2]. According to the two-process model of sleep regulation [3], the 24-h sleep–wake rhythm is dependent on the circadian rhythm (also named process C), generated by the internal clock located in the suprachiasmatic nucleus (SCN) of the hypothalamus. The SCN is already functioning at birth [4] and matures further in the following months under the influence of external zeitgebers such as light [5] and social time cues [6].

The two-process model consists of a second process – called process S – representing sleep homeostasis. According to the homeostatic regulation of sleep, sleep pressure increases during the waking period and decreases during sleep. Sleep homeostasis shows substantial maturational changes in the first months of life and still matures further on until middle childhood [7,8]. This developmental process can be seen by the consolidation of sleep period during the night and wake periods during the day occurring around the second month of life [1,7,9,10] and by the continuous decrease of total sleep duration over infancy [8]. It is suggested that the development of this process cannot be influenced by external factors, but reflects the maturation of intrinsic bioregulatory processes [8,11].

The time of emergence of a 24-h sleep–wake rhythm in *preterm* infants is still debated and is thought to develop either after a certain length of exposure to time cues [1,12–15] or after reaching a certain

Abbreviations: CA, post term corrected age; CL, cycled lighting; DL, dim lighting; GA, gestational age; LSP, longest consolidated sleep period between 12 pm an 6 am; PT, preterm; SCN, suprachiasmatic nucleus of the hypothalamus; SES, socioeconomic status; T, term.

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post term age needed for the development of intrinsic brain functions [2,16–19].

Previous studies either compared term infants to preterm infants without considering lighting condition [14,19,20], or preterm infants cared for in different lighting conditions were compared without a term control group [12,13,15,18,21–23]. The latter showed a positive effect of cycled light condition on the development of daily sleep rhythms, growth factors or state regulation such as activity measures [23], weight gain [15,21], sleep measures [13] or crying pattern [12]. As a result, cycled light regime is recommended by the American Academy of Pediatrics (AAP) and the American College of Obstetricians and Gynecologists (ACOG) as the standard care condition on neonatal wards since 1997 [24].

Shimada et al. [19] compared term and preterm infants and reported the occurrence of a 24-h sleep–wake rhythm at a mean age of 44.8 weeks gestational age in both groups. These authors concluded that the infant's innate biological clock needs to mature first until it is responsive to external time cues. We note, however, that the possibility of an earlier entrainment in preterm infants by cycled light during neonatal care was not addressed; preterm infants in this study were exposed to constant bright light. In contrast, Mc Millen et al. [14] found evidence that the length of exposure to environmental time cues (light–dark cycle and single caregiver) is essential. These authors showed that preterm infants exposed to environmental time cues after discharge (slightly before term equivalent age) entrained after identical time of exposure (preterm: 9.8 ± 2.2 wk, term 8.7 ± 2.7 wk), but reached entrainment at an earlier chronological age than term infants (preterm: 47.0 ± 2.2 wk, term: 48.9 ± 2.7 wk, $p < 0.05$). Also in this study preterm infants were cared for in constant bright light during neonatal hospitalization. It is important to consider that preterm infants cared for in a neonatal nursery are always exposed to various external factors influencing the development of a 24-h sleep wake rhythm. Hence, multiple caregivers and medical interventions at varying time points of the day may impair the development of a 24-h sleep–wake rhythm, while other factors such as regular infant care schedules like feeding on a 4- or 6 h interval or cycled light exposure can act as Zeitgeber for the developing rhythm [11].

With the assumption that a 24-h sleep–wake rhythm also emerges after birth in preterm infants and depends on the length of exposure to time cues, we combined both aspects and hypothesized that 1) preterm infants show an earlier emergence of a 24-h sleep–wake rhythm than term infants and 2) that this effect is more pronounced in preterm infants cared for in cycled light condition compared to dim light during their neonatal stay.

2. Methods

2.1. Population

Very preterm infants (≤32 0/7 weeks gestational age) were recruited at the Clinic Neonatology of the University Hospital Zurich, Switzerland. Term infants were recruited from the postnatal wards of the University Hospital Zurich. Primary exclusion criteria were major cerebral injuries (intraventricular hemorrhage grade III [25], periventricular leukomalacia or venous infarction [26]), retinopathy of prematurity grade III and IV, congenital malformations, small for gestational age at birth, prenatal infections or intrauterine drug exposure. Secondary exclusion criteria were participation in another clinical trial or parental language difficulties. 41 preterm infants (PT) and 22 term infants (T) were recruited. Later, 7 preterm and 8 term infants had to be excluded due to various reasons: drop out after first recording (reasons: too time consuming, stressful time, moving abroad; PT n = 2, T n = 4), incomplete diary (PT n = 4, T n = 4), and excessive crying behavior (PT n = 1). Thus, a total of 34 preterm (girls = 17) and 14 term infants (girls = 7) were included for the final analysis.

The ethics committee of the University Children's Hospital Zurich and the Canton Zurich approved the study protocol. The study was performed according to the Declaration of Helsinki. Written informed consent was obtained from all parents.

2.2. Procedures during hospitalization for preterm infants and lighting conditions

Preterm infants were part of an interventional trial (see for details [12]) and randomly assigned to either cycled light condition (CL) or dim light condition (DL). CL condition was characterized by lights on between 7 AM and 7 PM and off between 7 PM and 7 AM. Every bed was equipped with curtains, which were taken away during daytime periods and overhead room lights were turned on. For the DL condition – the standard condition on the ward – bed curtains were closed whenever the child was asleep or quiet and opened only for feeding periods every 3 or 4 h for a few minutes (for infants in an incubator, green quilts were used for cover).

Enrollment took place after the transfer from intensive to intermediate care, requiring stable condition of the child and available space in the intermediate care rooms, and lasted until discharge. Randomization was performed depending on availability of free space at the time of transfer or – in case of available space in both conditions – according to a table of random numbers (for more detailed information see [12]).

2.3. Procedures at home for preterm and term infants

At 5 and 11 weeks' post term corrected age (CA), parents had to fill in the Baby's Day Diary [27], coding for sleep within 5 minute intervals over 3 consecutive days. Furthermore, actigraphs were placed on the infant's ankle, fixed with a soft sleeve bandage and recorded over 10 consecutive days. At 25 weeks' CA, parents had to fill in a sleep diary, coding for sleep within 15-minute intervals over 10 consecutive days together with the actigraph recording. For the first recording parents were personally instructed at a face-to-face home visit. The following recordings were preceded by a telephone contact and data and actigraphs were sent by mail (for further details see [12]).

In addition, the type of feeding (fully breastfed, partially breastfed, bottle fed; nominal scaled) was asked at 5 and 11 weeks CA during a telephone interview with the parents.

2.4. Sleeping variables

Based on the sleep diary, mean total sleep duration per 24 h, mean sleep duration during the day (7 am–7 pm) and at nighttime (7 pm–7 am) and sleep day/night ratio were computed using a custom made Matlab routine (The MathWorks, Inc. Natick, MA). Furthermore, the longest consolidated sleep period at night (LSP) was calculated and averaged over the number of recorded days. LSP was defined as the longest sleep period within the hours between midnight and 6 AM and expressed in percentage of these 6 h (see [20]).

2.5. Activity variables

Activity scores were measured by the Actiwatch-mini® (Cambridge Neurotechnology, Cambridge, UK) at 5 weeks CA and the Actiwatch-AW4® at 11 and 25 weeks CA in 30 seconds epochs. Mean activity counts per 24 h ("total activity"), for the night (7 pm-7 am) and the daytime (7 am-7 pm) as well as the activity day/night ratio were calculated [23]. Days were excluded when data were missing for longer than two consecutive hours. Mean number of days of recording at 5, 11 and 25 weeks respectively were for preterm infants 8.7 d, 8.5 d and 8.4 d and for term infants 9.1 d, 9.2 d and 8.4 d.

2.6. Socioeconomic status

Socioeconomic status (SES) was estimated by means of a sum score of 2 standardized 6-point scales of paternal occupation and maternal education ranging from 2 (highest SES) to 12 (lowest SES). This measure was used in previous studies and was shown to be a reliable and valid indicator of SES in our community [28,29].

2.7. Statistical analysis

Descriptive results were presented as mean and standard deviation for continuous variables and as number of cases for nominal variables. Chi-square test was used to compare gender and type of feeding while all other variables were compared using Student's unpaired t-test (SPSS 14 OJ for Windows, SPSS Inc., Chicago, IL, USA). For the simultaneous analysis of age and group effects, mixed model analysis was used (S-PLUS 8.0 for Windows (Corp, Seattle, WA). First interactions between age and group effects were calculated, if no interactions occurred, separate effects for age and for group were analyzed. The main emphasis was to compare preterm infants versus term infants; therefore the grouping variables were "term" and "preterm" infants for the main analysis. For a second objective, preterm infants were analyzed according to the different lighting conditions (CL and DL) during neonatal stay and compared to term infants (grouping variables: term, preterm-CL, preterm-DL).

Using only two covariates because of the small sample size, the analysis was redone using linear mixed models [26]. For the depending variables "sleep at nighttime", "LSP" and "activity at nighttime" the two covariates were: "type of feeding" (trend to more fully breastfed term infants with 11 weeks CA) and "gender" (known sex differences for activity [30]) with no differences in results, therefore it is not presented in this paper.

3. Results

Birth variables of the 14 term infants and 34 preterm infants are shown in Table 1. Term and preterm infants differed significantly as expected in the birth variables, but not with respect to gender or socioeconomic status. The type of feeding (fully breastfed, partially breastfed or bottle-fed) tended to be different between preterm and term infants at 11 weeks CA ($\chi^2 = 4.86$, $p = 0.09$): at 11 weeks CA term infants tended to be more often fully breastfed than preterm infants. Differences for birth and growth variables of the two subgroups of preterm infants (CL and DL) are shown in Table 2. There was no difference in birth and growth variables and in length of hospital stay between the two subgroups. The two groups of preterm infants did not differ concerning type of feeding.

Sleeping and activity variables were compared between term and preterm infants at 5, 11, and 25 weeks (Table 3). No significant interactions between age and group were found for any variable, thus a separate analysis of the effects for age and group was possible. A significant age effect was observed for all variables. With increasing age, total sleep time slightly decreased with increasing nighttime sleep, decreasing daytime sleep, therefore lower day/night ratio and longer consolidated sleep period; activity overall increased with age, showing a higher day/night ratio with increasing age. A significant group effect between PT and T infants was found for "sleep at nighttime", "LSP", and "activity at nighttime". Preterm infants showed longer nighttime sleep duration, especially a longer consolidated sleep period and less nighttime activity compared to term infants at the same ages (see also Fig. 1).

Comparing sleeping and activity variables between term infants, preterm-CL and preterm-DL infants, using mixed model analysis, no interactions between age and group were found. A significant age effect for all variables was found and the same three variables showed significant group effects (Table 4). In Table 5 estimated mean differences are shown for those three variables. Preterm-CL and preterm-DL infants showed no main differences for all variables. For "sleep at nighttime" the difference between term infants and preterm-CL infants was greatest and for "LSP" both preterm groups showed the same differences to term infants. For "activity at nighttime" the differences between term infants and preterm-DL infants was greatest. Interestingly, it has to be mentioned that preterm-DL infants were not only the least active infants at nighttime but also over total 24 h.

Table 1
Mean and standard deviation for birth variables for preterm and term infants.

Variable	Preterm (n = 34)	Term (n = 14)
GA, wk	30.0 ± 1.8	39.7 ± 1.3
Birthweight, g	1372 ± 338	3534 ± 392
Birth length, cm	39.3 ± 3.1	50.4 ± 1.6
Head circumference at birth, cm	28.1 ± 2.4	35.2 ± 1.0
Male gender, n, [a]	17	7
SES (2–12), median (range), [a]	4 (2–8)	2.5 (2–8)
Breastfed, (full/partly/none) n, [a]		
At 5 weeks	20/4/10	12/1/1
At 11 weeks	15/9/10	11/1/2

GA = gestational age, SES = socioeconomic status.
[a] No significant differences ($p < 0.05$) were found.

Table 2
Mean and standard deviation for birth and growth variables for preterm infants in the cycled light and dim light group.

Variable	CL (n = 17)	DL (n = 17)
At birth		
GA, wk	30.6 ± 0.9	29.5 ± 2.3
Birthweight, g	1439 ± 299	1305 ± 369
Birth length, cm	40.2 ± 2.6	38.5 ± 3.4
Head circumference, cm	28.6 ± 1.5	27.6 ± 3.0
At beginning of exposure		
PMA, wk	32.1 ± 1.0	32.6 ± 1.5
Weight, g	1491 ± 244	1620 ± 323
At discharge		
PMA, wk	36.5 ± 1.1	37.1 ± 2.1
Weight, g	2431 ± 433	2418 ± 416
Length, cm	46.7 ± 2.4	46.6 ± 2.1
Head circumference, cm	32.8 ± 1.4	33.1 ± 1.6
Length of hospital stay, d	41.6 ± 10.9	53.1 ± 23.8
Length of exposure, d	30.8 ± 11.2	31.3 ± 13.8
Male gender, n	8	9
SES (2–12), median (range)	4 (2–8)	4 (2–6)
Breastfed (full/partly/none), n		
At 5 weeks	9/1/7	11/3/3
At 11 weeks	9/2/6	6/7/4

No significant differences ($p < 0.05$) were found.
GA = gestational age, PMA = post menstrual age, SES = socioeconomic status.

4. Discussion

Our results show that preterm infants, independent of light exposure type, exhibit longer nighttime sleep duration, especially a longer consolidated sleep period and less nighttime activity than term infants. Therefore, preterm infants present with a more mature 24-h sleep–wake rhythm than term infants at the same age. Furthermore, CL exposure had a positive effect on nighttime sleep duration. Therefore, preterm infants seem to be mature enough to entrain their 24-h sleep–wake rhythm right after birth. Exposure to time cues seems to play an important role in this process.

Our findings are in line with those of McMillen et al. [14] showing that preterm infants exposed to environmental time cues briefly before term equivalent age reached entrainment at an earlier chronological age than term infants. Importantly, our results are also in line with the results of Shimada et al. [19]. They also found a longer nighttime sleep period in preterm infants compared to term infants at 3 and 4 months CA and a higher LSP with 4, 5 and 11 months CA. Because the aim of these authors was to show that preterm infants cared for in constant

Table 3
Sleeping and activity variables at 5, 11 and 25 weeks CA for term and preterm infants.

	5 weeks [a]		11 weeks [a]		25 weeks [a]		group effect [b]
Variable	Term (n = 14)	Preterm (n = 34)	Term (n = 14)	Preterm (n = 34)	Term (n = 14)	Preterm (n = 34)	Term/Preterm
Total sleep, h/24 h	13.7 ± 0.2	14.1 ± 0.2	13.6 ± 0.2	14.0 ± 0.1	12.8 ± 0.1	13.2 ± 0.1	NS
Sleep at daytime, h	6.0 ± 0.1	5.8 ± 0.1	5.0 ± 0.2	4.8 ± 0.1	3.7 ± 0.2	3.5 ± 0.1	NS
Sleep at nighttime, h	7.7 ± 0.2	8.3 ± 0.1	8.6 ± 0.1	9.2 ± 0.1	9.1 ± 0.2	9.6 ± 0.1	P = 0.02
Sleep day/night ratio	0.8 ± 0.0	0.7 ± 0.0	0.6 ± 0.0	0.5 ± 0.0	0.4 ± 0.0	0.4 ± 0.0	NS
LSP [c]	52.4 ± 3.1	63.6 ± 2.6	67.5 ± 2.9	78.8 ± 2.4	70.5 ± 3.2	81.8 ± 2.2	P = 0.01
Total activity, activity count/24 h	108.2 ± 10.1	83.1 ± 7.9	183.8 ± 11.2	158.7 ± 8.5	299.7 ± 13.4	274.6 ± 10.9	NS
Activity at daytime, a.c./daytime	69.1 ± 8.4	54.3 ± 6.3	130.0 ± 8.6	115.2 ± 7.1	234.1 ± 11.1	219.3 ± 9.4	NS
Activity at nighttime, a.c./nighttime	39.0 ± 2.9	28.7 ± 2.2	53.8 ± 3.2	43.4 ± 2.3	65.6 ± 4.2	55.2 ± 3.1	P = 0.005
Activity day/night ratio	1.8 ± 0.2	1.9 ± 0.1	2.6 ± 0.2	2.7 ± 0.1	4.1 ± 0.3	4.2 ± 0.2	NS

a.c.: activity counts.
[a] Reported as expected mean ± standard error.
[b] Using mixed model analysis, NS: not significant, $p > 0.05$; no interactions occurred.
[c] Longest sleep period during the 6 h period between 12 pm and 6 am, in %.

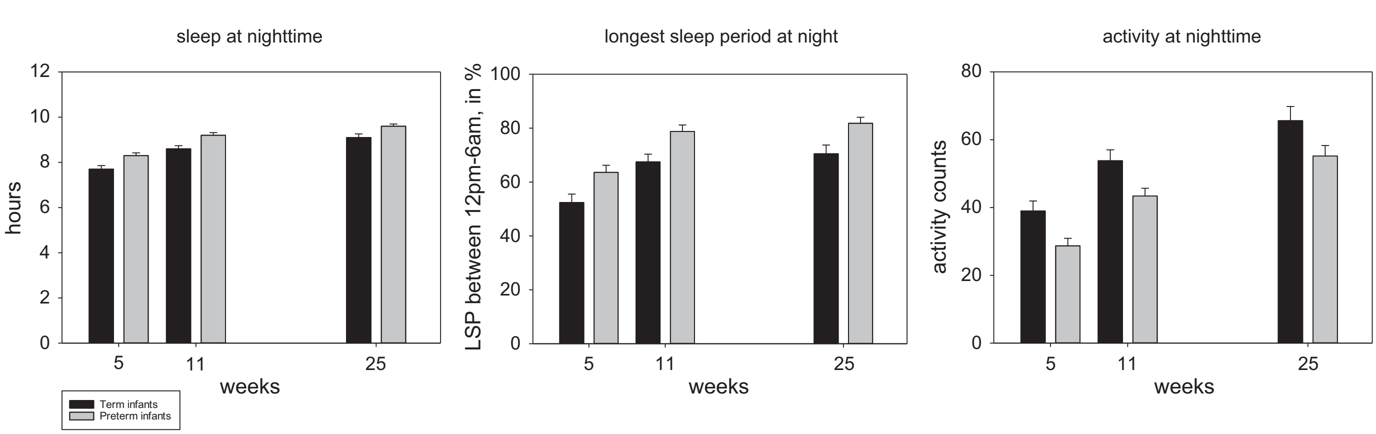
bright light during their neonatal stay were not *delayed* in the development of 24-h sleep–wake rhythm compared to term infants, they concluded that there were no differences between the groups. In fact, even the preterm infants in this study cared for in constant bright light showed a more mature 24-h sleep–wake rhythm than the term infants at equivalent ages. In contrast to other studies [13–15,23] the differences between the preterm-CL and preterm-DL group were not marked. Possible explanations could be that 1) sleep variables were not sensitive enough to detect small differences between the groups, 2) differences could have occurred at an earlier time point and were therefore missed in our study or 3) that other Zeitgebers also play an important role. In fact, we may conclude that all preterm infants had a benefit from external time cues. When focusing on the development of a 24-h sleep–wake rhythm, light as a time cue is needed for the timing of the internal clock [1,31] and can influence behavior state regulation by reducing fussing and crying episodes [12]. However, *social time cues* such as regular feeding, body contact while carrying an infant and daily routines giving a rhythm to daily life are known to play an even more important role [6] in establishing a 24-h sleep–wake rhythm. This observation may explain both, our result that there is no difference between preterm-CL and preterm-DL group and the results of Shimada et al. where bright light was the condition during hospitalization. In our study, term infants showed a trend to be more fully breastfed at 11 weeks of age compared to preterm infants at the corrected age. Because fully breastfed infants show more nighttime awakenings and tend to sleep through the night at a later time point compared to bottle fed infants [32], the analysis was redone using "type of feeding" as a covariate, but the findings did not change. We may, therefore conclude, that the type of feeding per se was not associated with the earlier emergence of a 24-h sleep–wake rhythm. However, we did not evaluate if infants were fed on demand or on a regular feeding pattern, which would have been a strong social time cue.

Evidence is accumulating that after preterm birth, the development of subcortically mediated processes such as some visual functions (ocular stability, tracking) may benefit from an earlier exposure to external stimuli whereas cortically mediated processes do not [33]. Therefore our result of an earlier entrainment of the 24-h sleep–wake rhythm in preterm infants – mediated at least partly by a subcortical pathway (namely the retinohyptohalamic pathway) – might be based on an earlier maturation of these pathways.

The strength of our study lies in the combination of the analysis of both term versus preterm infants and term infants versus preterm infants in the two lighting conditions (CL and DL). Also recording has taken place over a long time period until 25 weeks of (corrected) age.

Some limitations need to be mentioned when interpreting our results. First, the sample size was relatively small, but comparable to other studies [13–15,18]. Second, the studied preterm group included infants with no major brain injuries or other comprising factors and they were raised in families with medium to high socioeconomic status. Therefore, our results cannot be assigned to the general preterm population. Third, diaries differed between the ages 5/11 weeks CA (the Baby's Day Diary [27], 5-minute epochs, 5 different variables, three days of recording), and 25 weeks CA (sleep protocol, 15-minute epochs, 3 different variables, 10 days of recording). However, sleep variables are

Sleep at nighttime, longest sleep period at night and activity at nighttime at 5, 11 and 25 weeks CA for term and preterm infants



Group effect using mixed model analysis for all three variables p<0.05

Fig. 1. Sleep at nighttime, longest sleep period at night and activity at nighttime at 5, 11 and 25 weeks CA for term and preterm infants.

Table 4
Sleeping and activity variables at 5, 11 and 25 weeks CA for term, preterm-CL and preterm-DL infants.

	5 weeks [a]			11 weeks [a]			25 weeks [a]			Statistics[b]	
	T (n = 14)	PT-CL (n = 17)	PT-DL (n = 17)	T (n = 14)	PT-CL (n = 17)	PT-DL (n = 17)	T (n = 14)	PT-CL (n = 17)	PT-DL (n = 17)	Age effect	Group effect
Sleep at nighttime (h, decimal)	7.71 ± 0.2	8.41 ± 0.1	8.13 ± 0.1	8.63 ± 0.1	9.34 ± 0.1	9.05 ± 0.1	9.06 ± 0.2	9.77 ± 0.1	9.48 ± 0.1	P < 0.001	P = 0.04
LSP[c] (%)	52.36 ± 3.2	63.21 ± 3.1	64.05 ± 3.0	67.49 ± 3.1	78.35 ± 3.1	79.18 ± 2.9	70.49 ± 3.2	81.35 ± 2.8	82.18 ± 2.6	P < 0.001	P = 0.05
Activity at nighttime (a.c.)	39.05 ± 3.0	30.32 ± 3.1	27.16 ± 2.4	53.77 ± 3.4	45.03 ± 2.7	41.87 ± 2.8	65.57 ± 4.2	56.83 ± 3.6	53.68 ± 3.1	P < 0.001	P = 0.013

a.c.: activity counts.
[a] Reported as expected mean ± standard error.
[b] using mixed model analysis; no interactions occurred.
[c] longest sleep period during the 6 h period between 12 pm and 6 am, in %.

Table 5
Estimated mean differences of the three groups (Term, Preterm-CL, Preterm-DL).

	PT-CL − PT-DL [a]	T − PT-CL [a]	T − PT-DL [a]
Sleep at nighttime (h, decimal)	0.29 ± 0.2	−0.71 ± 0.2	−0.42 ± 0.2
LSP[b,] (%)	0.83 ± 3.5	−10.9 ± 3.8	−11.7 ± 3.4
Activity at nighttime (a.c.)	3.2 ± 3.7	8.7 ± 4.4	11.9 ± 4.2

[a] reported as mean differences ± standard error, using mixed model analysis, age independent analysis because of missing interactions.
[b] longest sleep period during the 6 h period between 12 pm and 6 am, in %.

in line with those of Shimada et al. [19] and activity variables with those of Eaton et al. [34].

In the presented study preterm infants showed a stronger 24-h sleep–wake rhythm than term infants at an equivalent age. We therefore conclude that the development of a 24-h sleep–wake rhythm starts right after birth and emerges after a certain length of exposure to time cues. Light and social time cues play an important role and preterm infants therefore benefit from an early and regular exposure to such time cues to establish and maintain a 24-h sleep–wake rhythm.

Conflict of interest statement

This is an unbiased study without conflicts of interest. All authors have made substantive contributions to this study in terms of conception and design, acquisition of data, analysis and interpretation of data and in drafting and revising the article. All authors give their final approval of the submitted version. The authors have otherwise nothing to declare. The Velux Foundation had no influence on study idea and design, recruitment of patients, data analysis, interpretation of results, writing of the manuscript and submission of the manuscript.

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References

[1] Rivkees SA. Emergence and influences of circadian rhythmicity in infants. Clin Perinatol Jun 2004;31(2):217–28.
[2] Shimada M, Takahashi K, Segawa M, Higurashi M, Samejim M, Horiuchi K. Emerging and entraining patterns of the sleep–wake rhythm in preterm and term infants. Brain Dev Oct 1999;21(7):468–73.
[3] Borbely AA. A two process model of sleep regulation. Hum Neurobiol 1982;1(3):195–204.
[4] Hao H, Rivkees SA. The biological clock of very premature primate infants is responsive to light. Proc Natl Acad Sci U S A Mar 2 1999;96(5):2426–9.
[5] Achermann. Mathematical models of sleep regulation. Front Biosci May 1 2003(8):s683–93.
[6] Lohr B, Siegmund R. Ultradian and circadian rhythms of sleep–wake and food-intake behavior during early infancy. Chronobiol Int Mar 1999;16(2):129–48.
[7] Jenni OG, Borbely AA, Achermann P. Development of the nocturnal sleep electroencephalogram in human infants. Am J Physiol Regul Integr Comp Physiol Mar 2004;286(3):R528–38.
[8] Jenni OG, LeBourgeois MK. Understanding sleep–wake behavior and sleep disorders in children: the value of a model. Curr Opin Psychiatry May 2006;19(3):282–7.
[9] Peirano P, Algarin C, Uauy R. Sleep–wake states and their regulatory mechanisms throughout early human development. J Pediatr Oct 2003;143(4 Suppl.):S70–9.
[10] Salzarulo P, Fagioli I. Post-natal development of sleep organization in man: speculations on the emergence of the 'S process'. Neurophysiol Clin Jun 1992;22(2):107–15.
[11] Adams SM, Jones DR, Esmail A, Mitchell EA. What affects the age of first sleeping through the night? J Paediatr Child Health Mar 2004;40(3):96–101.
[12] Guyer C, Huber R, Fontijn J, Bucher HU, Nicolai H, Werner H, et al. Cycled light exposure reduces fussing and crying in very preterm infants. Pediatrics Jul 2012;130(1):e145–51.
[13] Mann NP, Haddow R, Stokes L, Goodley S, Rutter N. Effect of night and day on preterm infants in a newborn nursery: randomised trial. Br Med J (Clin Res Ed) Nov 15 1986;293(6557):1265–7.
[14] McMillen IC, Kok JS, Adamson TM, Deayton JM, Nowak R. Development of circadian sleep–wake rhythms in preterm and full-term infants. Pediatr Res Apr 1991;29(4 Pt 1):381–4.
[15] Miller CL, White R, Whitman TL, O'Callaghan MF, Maxwell SE. The effects of cycled versus noncycled lighting on growth and development in preterm infants. Infant Behav Dev 1995;18(1):87–95.
[16] Coons S, Guilleminault C. Development of consolidated sleep and wakeful periods in relation to the day/night cycle in infancy. Dev Med Child Neurol Apr 1984;26(2):169–76.
[17] Mirmiran M. The function of fetal/neonatal rapid eye movement sleep. Behav Brain Res Jul-Aug 1995;69(1–2):13–22.
[18] Mirmiran M, Baldwin RB, Ariagno RL. Circadian and sleep development in preterm infants occurs independently from the influences of environmental lighting. Pediatr Res Jun 2003;53(6):933–8.
[19] Shimada M, Segawa M, Higurashi M, Akamatsu H. Development of the sleep and wakefulness rhythm in preterm infants discharged from a neonatal care unit. Pediatr Res Feb 1993;33(2):159–63.
[20] Anders TF, Keener M. Developmental course of nighttime sleep–wake patterns in full-term and premature infants during the first year of life. I. Sleep 1985;8(3):173–92.
[21] Brandon DH, Holditch-Davis D, Belyea M. Preterm infants born at less than 31 weeks' gestation have improved growth in cycled light compared with continuous near darkness. J Pediatr Feb 2002;140(2):192–9.
[22] Mirmiran M, Ariagno RL. Influence of light in the NICU on the development of circadian rhythms in preterm infants. Semin Perinatol Aug 2000;24(4):247–57.
[23] Rivkees SA, Mayes L, Jacobs H, Gross I. Rest-activity patterns of premature infants are regulated by cycled lighting. Pediatrics Apr 2004;113(4):833–9.
[24] American Academy of Pediatrics, Committee on Fetus and Newborn, American College of Obstetricians and Gynecologists, Committee on Obstetric Practice, March of Dimes Birth Defects Foundation. Guidelines for perinatal care4th ed. ; 1997 [Elk Grove Village, IL Washington, DC].
[25] Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. J Pediatr Apr 1978;92(4):529–34.
[26] Govaert P, De Vries LS. An atlas of neonatal brain sonography. 2nd ed. London: Mac Keith Press; 2010.
[27] Barr RG, Kramer MS, Boisjoly C, McVey-White L, Pless IB. Parental diary of infant cry and fuss behaviour. Arch Dis Child Apr 1988;63(4):380–7.
[28] Largo RH, Pfister D, Molinari L, Kundu S, Lipp A, Duc G. Significance of prenatal, perinatal and postnatal factors in the development of AGA preterm infants at five to seven years. Dev Med Child Neurol Aug 1989;31(4):440–56.
[29] Seitz J, Jenni OG, Molinari L, Caflisch J, Largo RH, Latal Hajnal B. Correlations between motor performance and cognitive functions in children born <1250 g at school age. Neuropediatrics Feb 2006;37(1):6–12.
[30] Campbell DW, Eaton WO. Sex differences in the activity level of infants1. Infant Child Dev 1999;8(1):1–17.

[31] Duffy JF, Czeisler CA. Effect of light on human circadian physiology. Sleep Med Clin Jun 2009;4(2):165–77.
[32] Galbally M, Lewis AJ, McEgan K, Scalzo K, Islam FMA. Breastfeeding and infant sleep patterns: an Australian population study. J Paediatr Child Health Feb 2013;49(2):E147–52.
[33] Ricci D, Cesarini L, Romeo DM, Gallini F, Serrao F, Groppo M, et al. Visual function at 35 and 40 weeks' postmenstrual age in low-risk preterm infants. Pediatrics Dec 2008;122(6):e1193–8.
[34] Eaton WO, McKeen NA, Campbell DW. The waxing and waning of movement: implications for psychological development. Dev Rev 2001;21(2):205–23.